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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,244	HO ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 27-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8,9,12,13 10
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicants' election without traverse of the Group II invention (claims 14-26) in Paper No. 16 filed 5/12/2003 is acknowledged. Claims 1-13 and 27-93 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 14-26 are under examination in the instant office action.

Information Disclosure Statement

Information disclosure statements filed on /26/2003 (IDS#8), on 5/21/2002 (IDS#9), on 1/14/2003 (IDS#12) and 2/11/2003 (IDS#13) have been considered. The corresponding forms PTO-1149 are attached herein.

Information disclosure statement filed on 3/07/2003 has been considered and placed into the file.

Claim Objections

Claims 14-26 are objected to because of the following informalities:

Claim 14 appears to contain some typing error such as "with" instead of "which". Appropriate correction is required.

Claim 21 appears to contain some typing errors such as the use of capital letter P for "p21" and "p53" (see specification page 32). It is suggested to use consistent and standard terminology. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 14-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite as related to a negative expression of bone sialoaprotein. According to the applicants' definitions "a substantially homogenous cell population" is a cell population having 70-100 % of cells which co-express CD49c and CD90 (page 7, par. 3). There are no particular definitions about expression of bone sialoprotein in the "substantially homogenous cell population". Thus, it is uncertain how much cells in the claimed product do not express bone sialoprotein. Are they within the substantially homogenous cell population or are they in addition to the substantially homogenous cell population? Thus, the components of the claimed product are uncertain.

Claim 26 is indefinite because it is uncertain as claimed and as disclosed whether the cells are capable to express the presently claimed factors/cytokines under appropriate conditions or whether the cells express the presently claimed factors/cytokines under the same conditions.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14-26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 14-26, as written, do not sufficiently distinguish over the cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences

between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated", for example, as taught by page 27 at line 7 of specification. See MPEP 2105.

Although "a substantially homogenous cell population" is defined as a cell population having at least 70 % of cells co-expressing CD49c and CD90 (page 7, line 9), the claimed invention is not limited to an isolated cell population. The co-expression of the claimed markers appear to be an inherent characteristic of a bone marrow cell population (page 27, lines 7-8) and, thus, the "substantially homogenous cell population" which co-express CD49c and CD90 does not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring bone marrow cell population.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14, 15, 19, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ross et al. [U].

Claims are drawn to a cell population which co-expresses CD49c and CD90 but does not express bone sialoprotein. Some claims are further drawn to the cells which express telomerase, do no express CD34 and/CD45 but express IL-6.

Ross et al. [U] disclose a human mesothelial cell population or a cell line wherein all cells (100%) co-express CD49c and CD90 (abstract or table 1) and wherein all cells are inherently do not express bone sialoprotein due to their mesothelial nature and source of origin (page 26, par. 2, line 6-8). The cells of the cited reference were cultured or propagated (page 26, par. 2) and, thus, they express telomerase at least to some extend since they are capable of proliferating as required for the product of claim 15. The cells of the cited reference have the potential to differentiate or they are capable undergo at least a terminal differentiation or cell death as required for the product of claim 19. The mesothelial cells of the cited reference do not express hematopoietic cell markers CD34 and/or CD45. The mesothelial cells of the cited reference are capable to express IL-6 (page 25, col. 2, last par.) as required for the claimed product (claim 26).

Thus, the cited reference clearly teaches all claimed limitations and, thus, it anticipates the claimed invention.

Claims 14-20 and 22-26 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2002/0168765 [IDS#12-AB3] or under 35 U.S.C. 102(a) as being anticipated by WO 01/34167 [IDS#8-AP] in the light of evidence by Cooper et al. [V] and US 5,837,539 [A].

Claims are drawn to a cell population which co-expresses CD49c and CD90 but does not express bone sialoprotein. Some claims are further drawn to the cells which express telomerase,

have a doubling time less than 48 hours, are capable to differentiate into a preselected phenotype including osteoblasts, are derived from human bone marrow and do no express CD34 and/CD45. Some claims are further drawn to the cells that express factors and/or cytokines including IL-6.

Both cited patents US 2002/0168765 [IDS#12-AB3] and WO 01/34167 [IDS#8-AP] contain the same subject matter and/or disclosure and, thus, for simplicity the disclosure of the WO publication is discussed. WO 01/34167 discloses a human bone marrow derived mixed cell population (page 45) comprising various subsets of mesenchymal stem cells which co-express CD90 and CD49 (integrin alpha chain) and which do not express CD34 and CD45 (Fig. 26). The isolated mixed populations of marrow stromal or mesenchymal stem cells of the cited patent are undifferentiated stem cells and, thus, they are reasonably expected do not express bone sialoprotein as the cells of the present invention. The cell populations of marrow stromal or mesenchymal stem cells are rapidly proliferating with a doubling time less than about 48 hours (see Fig. 20 or 22) as the claimed cells and, thus, they have a telomerase activity at least to some extend as required by the claimed invention. The cells of the cited patent are stem cells and, thus, they have a potential differentiate into preselected phenotypes including that are presently claimed (page 14, lines 20-22) and, therefore, they are reasonably expected to be capable to produce at least some factors and cytokines as the claimed cells under appropriate conditions due to their multipotentiality.

The following references are relied upon to support statements about inherent properties of bone marrow derived mesenchymal stem cell populations.

For example: the reference by Cooper et al. [V] clearly teaches that undifferentiated mesenchymal stem cells derived from bone marrow do not express bone sialoprotein (see

abstract). US 5,837,539 [A] is relied upon to demonstrate that the human mesenchymal stem cells (MSC) which are derived from bone marrow express all the following adhesion structures on a cell surface including integrins alpha 1 (CD49a), alpha 2 (CD49b), alpha 3 (CD49c) and alpha 5 (CD49e). (See table 5, at col. 39-40). The cited patent US 5,837,539 also teaches that MSCs express high levels of IL-6 in a basic and regular culture medium (col. 40, line 30).

Thus, the cited patens US 2002/0168765 [IDS#12-AB3] and WO 01/34167 [IDS#8-AP] are considered to anticipate the claimed invention since they disclose isolated stem cell populations derived from bone marrow mononuclear cells as the cells of the present invention and since they provide evidence that the isolated cells express the same properties as the presently claimed cells at least under appropriate culture conditions.

Claims 14-20 and 22-26 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/11011 [IDS#9-AL2] in the light of evidence by Cooper et al. [V] and US 5,837,539 [A].

Claims are drawn to a cell population which co-express CD49c and CD90 but does not express not bone sialoprotein. Some claims are further drawn to the cells which express telomerase, have a doubling time less that 48 hours, are capable to differentiate into a preselected phenotype including osteoblasts, chondrocytes and neuronal cell types. Some claims are further drawn to the cells that are derived from human bone marrow and do no express CD34 and/CD45. Some claims are further drawn to the cells that express factors and cytokines including MCP-1 and/or IL-6.

WO 01/11011 discloses a population of multipotent adult stem cells (MASC) derived from bone marrow mononuclear cells (page 25, lines 20-25 or page 71, example 1) which co-

express CD90 and CD49 (integrin alpha chain) and which do not express CD34 and CD45 (page 8, lines 24-30 or page 73). The MASC population is a population of undifferentiated stem cells and, thus, they are reasonably expected do not express bone sialoprotein as the cells of the present invention. The MASCs are rapidly proliferating with a doubling time 36-48 hours (page 24, line 20) or 48-60 hours (page 73, line 13). The MASCs have telomerase activity (page 16, par. 2). The MASCs have a potential differentiate into preselected phenotypes including that are presently claimed (page 9, lines 5-10). The MASCs are demonstrated to express MCP1 (page 26, line 12) and they are reasonably expected to be capable to produce other factors and/or cytokines as required for the claimed cells under appropriate conditions due to their multipotentiality.

The following references are relied upon to support the statement about inherent properties of bone marrow derived mesenchymal stem cell populations.

For example: the reference by Cooper et al. [V] clearly teaches that undifferentiated mesenchymal stem cells derived from bone marrow do not express bone sialoprotein (see abstract). US 5,837,539 [A] is relied upon to demonstrate that the human mesenchymal stem cells (MSC) derived from bone marrow express all the following adhesion structures on a cell surface including integrins alpha 1 (CD49a), alpha 2 (CD49b), alpha 3 (CD49c) and alpha 5 (CD49e). (See table 5, at col. 39-40). The cited patent US 5,837,539 also teaches that MSCs express high levels of IL-6 (col. 40, line 30).

Thus, the cited patent WO 01/11011 [IDS#9-AL2] is considered to anticipate the claimed invention since it discloses an isolated stem cell population derived from bone marrow mononuclear cells as the cells of the present invention and since it provides evidence that the

isolated stem cells express the same properties as the presently claimed cells at least under appropriate culture conditions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0168765 [IDS#12-AB3], WO 01/34167 [IDS#8-AP] and WO 01/11011 [IDS#9-AL2] in the light of evidence by Cooper et al. [V] and US 5,837,539 [A] taken with Christian van den Bos et al. [X] and Gartel et al. [W].

Claims 14-20 and 22-26 as explained above. Claim 21 is further drawn to the cells characterized by specific amounts of p21 and p53 transcripts.

The cited patens US 2002/0168765 [IDS#12-AB3] or WO 01/34167 [IDS#8-AP] or WO 01/11011 [IDS#9-AL2] are relied upon as explained above taken with the references by Cooper et al. [V] and US 5,837,539 [A].

Although the cited patents US 2002/0168765 [IDS#12-AB3] or WO 01/34167 [IDS#8-AP] do not clearly teach expression of factor such as MCP-1, the cited patent WO 01/11011 teaches expression of this factor by the same mesenchymal stem cell population derived from bone marrow.

Although the cited references Cooper et al. [V] and US 5,837,539 [A] do not clearly discloses expression of all cell surface adhesion structures, for example: CD90, by mesenchymal

stem cells or doubling time for mesenchymal stem cells, they appear to teach the mesenchymal stem cell population derived from human bone marrow mononuclear cells as the cells of the present invention and, thus, the cell populations of the cited references Cooper et al. [V] and US 5,837,539 [A] are obvious to those of ordinary skill in the art within the meaning of USC 103.

The cited references US 2002/0168765 [IDS#12-AB3], WO 01/34167 [IDS#8-AP], WO 01/11011 [IDS#9-AL2], Cooper et al. [V] and US 5,837,539 [A] are lacking particular disclosure related to the amounts of p21 and p53 transcripts in the cell populations of the mesenchymal stem cells.

However, the reference by Christian van den Bos et al. [X] teaches that human mesenchymal stem cells from bone marrow express p21 and that the particular amounts are related to specific culture conditions, for example: cell density during culturing and/or cell commitment for differentiation. The reference by Gartel et al. [W] is relied upon to demonstrate that the expression of p21 and of p53 are related events in the cell cycle progression (page 281).

Therefore, although the referenced cell populations of the cited US 2002/0168765 [IDS#12-AB3], WO 01/34167 [IDS#8-AP], WO 01/11011 [IDS#9-AL2], Cooper et al. [V] and US 5,837,539 [A] as disclosed might not be identical to the presently claimed cell population with regard to the expression and amounts of p21 and p53 transcripts, the differences between that which are disclosed and that which are claimed are considered to be so slight that the referenced cell populations are likely to possess the same characteristics of the claimed cell population particularly in view of the similar characteristics which they have been shown to share as explained above. Thus, the claimed cell population would have been obvious to those of

ordinary skill in the art within the meaning of USC 103. Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The substantially homogenous cell population of the present invention is an isolated bone marrow derived mononuclear cell population which has been characterized with markers of the adhesion structures CD90 and CD49e (examples 1and 2 on pages 25-28; particularly page 27, par. 1 or page 28, par. 1) but it is not a cell population separated (enriched) by a cell sorting based on the expression of CD90 and CD49c. Thus, the cells of the cited references which are homogenous mesenchymal stem cell population isolated from the same source such as human bone marrow mononuclear cells are the same or similar cells as the claimed cells.

With regard to the expression of p21 and p53 it appears that the claimed invention either (i) does not require any expression of p21 and p53 (from zero to 20000 or from zero to up to 3000 as claimed) or (ii) the claimed ranges are so large that they provide for include all types of stem cell multipotentiality since the critical amounts which are disclosed (specification page 32, line 11 and line 16) fall within the claimed ranges. Thus, the meaning of the claimed ranges allow for any amounts of p21 and p53 as related to the functional expression of stem cell multipotentiality and/or progression through the differentiation.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

AU 1651

July 22, 2003

PATENT EXAMINER

VERA AFREMOVA